ORIGINAL ARTICLE

Effectiveness of pre-operative routine blood tests in predicting complicated acute appendicitis

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ABSTRACT

BACKGROUND: Early prediction and diagnosis of perforation in acute appendicitis allow surgeons to choose the most appropriate treatment. The purpose of this study is to evaluate whether pre-operative routine laboratory examinations have a role in predicting complicated acute appendicitis.

METHODS: In the study, 783 patients operated with the diagnosis of acute appendicitis between the years 2014 and 2019 were analyzed retrospectively. Among the patients with non-perforated and perforated acute appendicitis, pre-operative laboratory tests include leukocyte (WBC), neutrophil, lymphocyte, platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), C-reactive protein (CRP), and neutrophil-to-lymphocyte rate (NLR) parameters were compared.

RESULTS: Appendicitis was not detected histopathologically in 81 cases. In the study, 89.9% (n=631) of the 702 patients were non-perforated and 10.1% (n=71) were perforated acute appendicitis cases. Perforation rate was higher in elderly patients (p<0.01). It was seen that lymphocyte count was significantly lower in the perforated group, and CRP and NLR were significantly higher (p=0.048, p=0.001, p=0.028, respectively). In the diagnosis of perforated acute appendicitis, cutoff values were 44.0 mg/dL for CRP, 7.65 for NLR and 1.7/mm^3 for lymphocytes. There was no statistical difference between the groups in terms of WBC, neutrophil, PLT, MPV, and PDW values.

CONCLUSION: Low lymphocyte count, high CRP, and high NLR were found to be reliable and strong predictive parameters in the diagnosis of complicated acute appendicitis.

Keywords: Complicated appendicitis; C-reactive protein; lymphocyte; neutrophil-to-lymphocyte rate.

INTRODUCTION

Acute appendicitis is the most common surgical emergency that causes acute abdomen in all age groups and requires prompt intervention.[1] The lifetime risk of developing appendicitis is 8.6–12% in men and 6.7–23.1% in women.[1,2] Although there are many diagnostic modalities such as the evaluation of well-defined clinical symptoms, scoring systems,[3,4] and radiological imaging, difficulties may be experienced preoperatively in both diagnosing appendicitis and determining whether complications develop.

Although surgical intervention continues to maintain its priority in treatment, it has been shown that antibiotics can be effective and safe in the treatment of uncomplicated appendicitis due to the development in antibiotherapy.[5,6] The importance of determining the prevalence of appendicitis has increased with the use of antibiotics as a treatment option. In recent studies, the prevalence of appendicitis and the possibility of perforation in the emergency department such as leukocyte, neutrophil, platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), neutrophil lymphocyte ratio (NLR), and C-reac-

Cite this article as: Uludağ SS, Akıncı O, Güreş N, Tunç E, Erginöz E, Şanlı AN, et al. Effectiveness of pre-operative routine blood tests in predicting complicated acute appendicitis. Ulus Travma Acil Cerrahi Derg 2022;28:1590-1596.

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Ulus Travma Acil Cerrahi Derg 2022;28(11):1590-1596 DOI: 10.14744/tjtes.2021.13472 Submitted: 25.05.2021 Revised: 22.06.2021 Accepted: 23.08.2021

tive protein (CRP) has been shown to be predictable and correlated with the laboratory parameters used in routine practice.[7–9] Parameters such as NLR are important in prioritizing patients for surgery and useful for patients who do not undergo radiological imaging modality.[10] NLR has also been shown to have high accuracy for the diagnosis of complicated appendicitis.[11] In the end, laboratory parameters, when combined with routine physical examination and imaging modalities, are useful and may help clinical diagnose acute appendicitis.[12]

In this study, we aimed to evaluate the effectiveness of routine pre-operative blood tests of patients who underwent appendectomy with a diagnosis of acute appendicitis in the prediction and diagnosis of complicated acute appendicitis.

MATERIALS AND METHODS

In the study, 783 patients who were operated with a prediagnosis of acute appendicitis in İstanbul University Cerrahpaşa Faculty of Medicine General Surgery Clinic between January 2014 and July 2019 were analyzed retrospectively. Patients under 18 years of age and 81 patients without acute appendicitis as a result of the pathological evaluation of the appendectomy specimen were accepted as appendectomy-negative and were excluded from the study. Ethics committee approval was obtained for the study (approval number: 03.03.2020/83045809).

The diagnosis of acute appendicitis in our hospital was established based on clinical manifestation, physical examination, laboratory findings, abdominal ultrasound, and/or computerized tomography. The final diagnosis was established by histopathological findings. Age, gender, body mass index (BMI), WBC, neutrophil, lymphocyte, PLT, MPV, PDW, NLR, and CRP values of the patients were recorded. Appendectomy specimens of patients diagnosed with acute appendicitis both clinically and pathologically were classified as phlegmonous, gangrenous, and perforated appendicitis found on pathology reports. The cases were divided into two groups as perforated and non-perforated. Age, gender, BMI, WBC, neutrophil, lymphocyte, PLT, MPV, PDW, NLR, and CRP values were statistically compared between these two groups.

Number Cruncher Statistical System (NCSS) (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum) were used while evaluating the study data. The suitability of the quantitative data to normal distribution was tested by Kolmogorov–Smirnov, Shapiro–Wilk test, and graphical evaluations. Student's t-test was used for two-group comparisons of quantitative data with normal distribution, and Mann–Whitney U-test was used for two-group comparisons of data not showing normal distribution. Pearson's Chi-square test was used to compare qualitative data. Diagnostic screening tests (sensitivity, specificity, PKD, and NKD) and receiver operating characteristic (ROC) curve analysis were used to determine cutoff values for statistically significant parameters. Significance was assessed at least at $p<0.05$ level.

RESULTS

This study was performed in İstanbul University Cerrahpaşa Faculty of Medicine General Surgery Clinic between the years of 2014 and 2019. The demographic information of the patients is shown in Table 1.

Table 1. Evaluation of the demographic characteristics of the cases

		Total (n=702)	Diagnosis		p
			Non-Perforated Group (n=631)	Perforated Group (n=71)	
Age (year)	Min-Max (Median)	6–95 (37)	6–95 (36)	21–81 (42)	[a]0.003 (p<0.01)
	Mean±Standard deviation	40.37±15.58	39.79±15.45	45.54±15.87	
Sex; n (%)	Women	288 (41.0)	259 (41.0)	29 (40.8)	[b]0.974
	Men	414 (59.0)	372 (59.0)	42 (59.2)	
BMI (kg/m^2)	Min-Max (Median)	17.5–42.4 (25.8)	17.5–42.4 (25.8)	18.1–41.4 (25.4)	[a]0.604
	Mean±Standard deviation	26.06±4.98	26.09±4.93	25.77±5.40	
	Underweight	17 (2.4)	15 (2.4)	2 (2.8)	
	Normal body weight	294 (41.9)	264 (41.8)	30 (42.3)	
	Overweight	270 (38.5)	242 (38.4)	28 (39.4)	
	Obese	121 (17.2)	110 (17.4)	11 (15.5)	

[a]Student t-test; [b]Pearson Chi–Square Test. BMI: Body mass index.

The mean age of the perforated appendicitis group was found to be significantly higher than the non-perforated group (p=0.003). No statistically significant relationship was found between the two groups in terms of gender distribution and BMI of the patients (Table 1).

A statistically significant difference was found between the ages of the cases based on the diagnosis of perforated appendicitis (p=0.003; p<0.01). The age of those diagnosed with perforated appendicitis is higher.

Gender distribution and BMI measurements of the cases on the status of perforated appendicitis diagnosis did not show statistically significant difference (p>0.05).

As a result of the histopathological evaluation of the appendectomy materials of the patients, 35.1% of the cases (n=81) were diagnosed with acute appendicitis, 35.2% with phlegmonous appendicitis (n=247), 8.1% with gangrenous appendicitis (n=57), and 10.1% with perforated appendicitis (n=71). Perforation was not observed in 89.9% (n=631) of the cases. Of the patients, 11.5% did not receive a diagnosis of appendicitis.

CRP and NLR measurements of patients with a diagnosis of perforated appendicitis were found to be significantly higher than those without a diagnosis of perforated appendicitis (Table 2). Based on this significance, it was considered to calculate the cutoff point for CRP and NLR. ROC analysis and diagnostic screening tests were used to determine the cutoff point for the groups.

Leukocyte, Neutrophil, PLT, MPV, and PDW measurements of the cases did not show statistically significant difference for the diagnosis of perforated appendicitis (p>0.05). A statistically significant difference was found between lymphocyte measurements of the patients from to the status of perforated appendicitis (p=0.048; p<0.05); lymphocyte measurements of those diagnosed with perforated appendicitis are

Table 2. Comparison of pre-operative laboratory findings between groups

		Diagnosis		p
		Perforated appendicitis (-)	Perforated appendicitis (+)	
Leukocyte	n	631	71	
	Min-Max (Median)	0.4–413 (12.8)	5.2–23.3 (13.3)	[b]0.272
	Mean±Standard deviation	13.33±16.49	13.29±4.39	
Neutrophil	n	629	71	
	Min-Max (Median)	0–133 (9.8)	2.9–21.1 (10.4)	[b]0.143
	Mean±Standard deviation	9.99±6.51	10.61±4.40	
Platelet	n	631	71	
	Min-Max (Median)	3.7–723 (244)	34.7–507 (250)	[b]0.947
	Mean±Standard deviation	249.13±71.95	249.84±80.12	
Mean platelet volume n	631	70		
	Min-Max (Median)	5.6–13 (8.2)	6.4–11.4 (8.1)	[a]0.570
	Mean±Standard deviation	8.43±1.23	8.34±1.22	
Platelet distribution width	n	631	70	
	Min-Max (Median)	6.8–203 (16.7)	11.6–19.7 (16.7)	[b]0.793
	Mean±Standard deviation	16.57±7.64	16.65±1.04	
Lymphocyte	n	625	70	
	Min-Max (Median)	0.1–92.4 (1.7)	0.4–3.5 (1.6)	[b]0.048*
	Mean±Standard deviation	1.99±3.72	1.64±0.76	
C-reactive protein n	614	69		
	Min-Max (Median)	0.1–518 (17.8)	1–530 (68)	[b]0.001**
	Mean±Standard deviation	43.81±69.59	103.07±113.33	
Neutrophil-to-lymphocyte rate	n	625	70	
	Min-Max (Median)	0.3–73 (5.3)	1.1–32.7 (7.4)	[b]0.028*
	Mean±Standard deviation	7.58±8.02	8.50±6.57	

[a]Student t-test; [c]Mann-Whitney U Test; **p<0.01; *p<0.05.

lower. Furthermore, a statistically significant difference was found between the CRP measurements of the cases according to the diagnosis of perforated appendicitis (p=0.001; p<0.01). CRP measurements of those diagnosed with perforated appendicitis are higher. A statistically significant difference was also found between the NLR measurements of the cases according to the status of the perforated appendicitis diagnosis (p=0.028; p<0.05). NLR measurements of those diagnosed with perforated appendicitis are higher.

In the pre-operative blood tests of the perforated group, it was observed that the average of CRP and NLR values was statistically higher than the non-perforated group (p=0.001; p=0.028, respectively). Based on this significance, ROC analysis and diagnostic screening tests were performed, and cutoff values for CRP and NLR were calculated (Table 3). The cutoff point for CRP in the diagnosis of perforated appendicitis was found to be ≥44. For the CRP ≥44 cutoff value; sensitivity was 60.87%, and specificity was 71.82%, positive predictive value was 19.53%, negative predictive value was 94.23%, and accuracy was 70.72% (Table 3). The underlying area of the obtained ROC curve was calculated as 70.3%, and standard error as 3.4%.

The NLR cutoff point for the diagnosis of perforated appendicitis was ≥7.61. For 7.61 cutoff value of NLR measurement; sensitivity is 50.00%, specificity is 67.36%, positive predictive value is 14.64%, negative predictive value is 92.32%, and accuracy is 65.61%. The underlying area of the ROC curve obtained was 58.0%, standard error was 3.5% (Table 3).

A statistically significant relationship was found between the diagnosis of perforated appendicitis and the cutoff value of 7.61 for the NLR level (p=0.004). The risk of perforation appendicitis is 2.064 times higher in patients with an NLR level of 7.61 and above. The ODDS ratio for NLR is 2.064 (95% CI: 1.255–3.394) (Table 4).

The cutoff point for lymphocyte was found to be 1.7 and below, depending on their perforated appendicitis diagnosis. For the 1.7 cutoff value of lymphocyte measurement; sensitivity is 64.29%, specificity is 50.08%, positive predictive value is 12.61%, negative predictive value is 92.60%, and accuracy is 51.51%. The area under the obtained ROC curve was 57.2%, standard error of 3.5% (Table 3).

A statistically significant relationship was found between the perforated appendicitis diagnosis and the cutoff value of 1.7 for lymphocyte level (p=0.023; p<0.05). In patients with lymphocyte level 1.7 and below, the risk of having perforated

Table 3. Diagnostic screening tests and ROC Curve results for CRP and NLR in the prediction of perforated appendicitis

	Diagnostic Scan					ROC Curve		p
	Cut-off	Sensitivite	Spesifisite	Positive Predictive Value	Negative Predictive Value	Area	95% Confidence Interval	
CRP	≥44	60.87	71.82	19.53	94.23	0.703	0.636–0.769	0.001**
NLR	≥7.61	50.00	67.36	14.64	92.32	0.580	0.512–0.648	0.028*
Lymphocyte	≤1.7	64.29	50.08	12.61	92.60	0.572	0.503–0.640	0.048*

ROC: Receiver operating characteristic; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte rate.

Table 4. Relationship between the diagnosis of perforated appendicitis and CRP and NLR (cut-off values)

		Diagnosis				p	Odds (%95 CI)
		Perforated appendicitis (-)		Perforated appendicitis (+)			
		n	%	n	%		
CRP	<44	441	71.8	27	39.1	0.001**	3.965
	≥44	173	28.2	42	60.9		(2.371–6.633)
NLR	<7.61	421	67.4	35	50.0	0.004**	2.064
	≥7.61	204	32.6	35	50.0		(1.255–3.394)
Lymphocyte	>1.7	313	50.1	25	35.7	0.023*	1.806
	≤1.7	312	49.9	45	64.3		(1.081–3.017)

Pearson Chi-Squared Test; **p<0.01. CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte rate; CI: Confidence interval.

appendicitis (+) is 1806 times higher. The ODDS ratio for lymphocyte is 1.806 (95% CI: 1.081–3.017) (Table 4).

DISCUSSION

Since acute appendicitis is the most common cause of acute abdomen and the most common abdominal pathology requiring emergency surgery, the primary goal of surgeons is to make the correct diagnosis and to minimize the negative laparotomy rate as much as possible. However, the diagnosis of acute appendicitis can still be challenging in some cases due to the absence of clinical findings or negative laboratory findings. Therefore, scoring systems, the most popular of which are ALVARADO and RIPASA, have been developed in which clinical and laboratory findings are combined.[3,4,13]

Although there are studies suggesting conservative treatments for uncomplicated appendicitis,[14,15] there are studies suggesting interval appendectomy after non-operative approach for complicated acute appendicitis (CAA).[16] The most important pre-diagnostic examination used in this distinction is abdominal computed tomography (CT), which significantly reduced the negative appendectomy rate after its introduction. Its sensitivity and specificity in diagnosis are 95% and 94%, respectively.[17] In CT imaging, findings such as extraluminal appendicolith, abscess, appendiceal wall enhancement defect, extraluminal air, ileus, periappendiceal fluid collection, ascites, and intraluminal air are important in favor of complicated appendicitis. Despite the power of CT in diagnosis, complicated appendicitis may not be predicted in approximately 18% of cases.[18] Therefore, other predictive factors of the patient that will accompany the CT findings in the diagnosis of CAA have begun to be investigated. Factors such as late presentation, epigastric pain, advanced age, high education level, and being married have been reported as risk factors for CAA.[19] In our study, it was seen that the increase in patient age is a significant risk factor for complicated appendicitis.

C-reactive protein is an indicator, which rises in acute phase with progressing inflammation in many illnesses. In one meta-analysis study, specificity and sensitivity of CRP's diagnostic accuracy had been designated in a wide range.[20] Avanesov et al. defined an appendicitis severity index where they combined CT findings with parameters such as CRP and WBC, and found the positive predictive value of the index for complicated acute appendicitis to be 92%.[21] In many studies in the literature, it has been shown that the increased CRP level is a valuable and feasible marker in the differentiation of non-complicated and complicated appendicitis.[22–24] CRP values over 44 mg/dL had been obtained as meaningful for complicated appendicitis in our study.

NLR is a laboratory parameter with acceptable sensitivity and specificity, which has been shown to be effective in various studies in the differentiation of complicated/uncomplicated acute appendicitis in recent years.[10,25] Although different cutoff points are revealed in the studies, it is important to consider that a simple hemogram test aids in the diagnosis of CAA without including the CRP cost. In our study, we concluded that high NLR (≥7.65) was effective in predicting perforated appendicitis.

The white blood cell count may not be sufficient to predict CAA due to its wide range of sensitivity and specificity. Virmani et al. reported the cutoff value for CAA to be WBC count over 13.500/mm^3, while Atema et al. reported this number to be over 13,000/mm^3.[26,27] On the contrary, in our study, no significant difference was found between perforated and non-perforated groups in terms of WBC.

In our study, we also observed that the isolated lymphocyte count decreased significantly in CAA cases. Similarly, in the literature, it has been argued that low lymphocyte count is a more valuable parameter than WBC and NLR in the diagnosis of complicated appendicitis due to its high sensitivity and specificity.[26,28]

Aydogan et al. reported that PLT, MPV, and PDW are valuable and useful markers for detecting perforation in acute appendicitis.[10] On the other hand, Pehlivanlı et al. reported that PLR, but not PLT and MPV, was significant in the distinction between perforated/non-perforated appendicitis.[29] In our study, no significant relationship was found between the parameters of PLT, MPV, and PDW and complicated acute appendicitis.

There were some limitations in this study. First, the current systemic biomarkers such as CRP/albumin, platelet/lymphocyte ratio, neutrophil gelatinase-associated lipocalin (NGAL), IL-6, and monocyte/lymphocyte ratio were not included in the study. Second, this was a retrospective study that took place in a single institution. A strong feature of this study is the large patient size and the fact that these biomarkers can be used in the outpatient routine, eliminating the need for funding. We believe that our results support the current findings in the literature.

Conclusion

Low lymphocyte count, high CRP, and NLR level are useful, cheap in cost, reliable, and are valuable laboratory parameters in predicting complicated acute appendicitis. It is a fact that multi-center, prospective, and clinical studies involving large patient groups on the subject are needed.

Ethics Committee Approval: This study was approved by the İstanbul University-Cerrahpaşa Cerrahpaşa Faculty of Medicine Clinical Research Ethics Committee (Date: 03.03.2020, Decision No: 83045809).

Peer-review: Internally peer-reviewed.

Authorship Contributions: Concept: E.E., O.A., A.K.Z., A.N.Ş., M.F.Ö.; Design: E.E., E.T., O.A., S.S.U.; Supervision:

E.T., A.K.Z., A.N.Ş., S.S.U.; Resource: A.K.Z., S.S.U.; Materials: O.A., E.T., S.S.U.; Data: O.A., E.T., S.S.U.; Analysis: N.G., E.T., M.F.Ö.; Literature search: N.G., E.E., S.S.U., A.H.Ş.; Writing: E.E., A.K.Z.; Critical revision: N.G., A.K.Z., M.F.Ö.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study has received no financial support.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Komplike akut apandisiti öngörmede ameliyat öncesi rutin kan testlerinin etkinliği

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AMAÇ: Akut apandisitte perforasyonun erken tahmini ve teşhisi cerrahların en uygun tedaviyi seçmesine olanak tanır. Bu çalışmanın amacı, ameliyat öncesi rutin laboratuvar incelemelerinin komplike akut apandisiti öngörmede rolü olup olmadığını değerlendirmektir.

GEREÇ VE YÖNTEM: Çalışmada 2014–2019 yılları arasında akut apandisit tanısı ile ameliyat edilen 783 hasta geriye dönük olarak incelendi. Perfore olmayan ve perfore akut apandisiti olan hastalar arasında ameliyat öncesi laboratuvar testleri arasında lökosit (WBC), nötrofil, lenfosit, trombosit (PLT), ortalama trombosit hacmi (MPV), trombosit dağılım genişliği (PDW), C-reaktif protein bulunur. Çalışmada CRP ve nötrofil-lenfosit oranı (NLR) parametreleri karşılaştırılmıştır.

BULGULAR: Toplam 81 olguda histopatolojik olarak apandisit saptanmamıştır. Çalışmada 702 hastanın %89.9'u (n=631) perfore bulunmamıştır, %10.1'i (n=71) perfore akut apandisit tanısı almıştır. Yaşlı hastalarda perforasyon oranı daha yüksek bulunmuştur ($p<0.01$). Lenfosit sayısının perfore grupta anlamlı olarak daha düşük olduğu, CRP ve NLR'nin anlamlı olarak yüksek olduğu görüldü (sırasıyla $p=0.048$, $p=0.001$, $p=0028$). Perfore akut apandisit tanısında eşik değerleri CRP için 44.0 mg/dL, NLR için 7.65 ve lenfositler için 1.7/mm^3 idi. Gruplar arasında WBC, nötrofil, PLT, MPV ve PDW değerleri açısından istatistiksel olarak fark yoktu.

TARTIŞMA: Düşük lenfosit sayısı, yüksek CRP ve yüksek NLR, komplike akut apandisit tanısında güvenilir ve güçlü prediktif parametreler olarak bulunmuştur.

Anahtar sözcükler: CRP; komplike apandisit; lenfosit; NLR.

Ulus Travma Acil Cerrahi Derg 2022;28(11):1590-1596 doi: 10.14744/tjtes.2021.13472